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Responsible Care in the Face of Shifting Recommendations and Imperfect Diagnostics for Zika Virus

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The US Centers for Disease Control and Prevention (CDC) recently released updated interim guidance for when pregnant women should receive serologic testing for the Zika virus.¹ The circumstances within which these recommendations emerge are complex: the public concern about the Zika virus is declining, the severity of epidemics around the globe is abating, and as a critical consideration in the development of recommendations, the rate of false-positive Zika virus test results (and the consequential unnecessary anxiety) is high.

After more than 12 months of recommending serologic testing for all Zika-exposed pregnant women regardless of the nature, timing, and duration of exposure or symptoms, the CDC now recommends testing only for pregnant women who present with symptoms consistent with Zika infection or those with ongoing Zika exposure throughout pregnancy. The reasons cited by the CDC for these changes are sound from a public health standpoint and may help mitigate the risks associated with inflated rates of false-positive diagnoses. However, the new recommendations create challenges and complexities for the context of clinical care, as nuanced decisions about (and responsibilities for) testing of asymptomatic patients are now transferred to clinicians and patients, particularly in areas lacking jurisdiction-specific recommendations.

For the clinical community, the shift entails issues not just of standard clinical practice, but of ethics. Clinicians can no longer simply follow the CDC recommendations that many have

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come to appreciate for their universality. Instead, the CDC now recommends that clinicians use a shared decision-making model, taking into account patients' values and preferences in considering whether to be tested for Zika virus infection during pregnancy. Although often a welcome approach, especially in highly value-laden clinical contexts in which some clinical decisions are made not just based on facts but on the interpretation of the facts through the lens of a person's values or set of beliefs, the introduction of shared decision-making as an approach to Zika testing for asymptomatic pregnant women may have several significant, if inadvertent, consequences.

First is the possibility that access to testing for those who would benefit might be constrained. As discretion regarding testing shifts to the clinical setting, clinician expertise and patient preference will be major factors in any discussion around Zika virus testing. Notably, shared decision-making models in health care tend to accord a higher value to patients who are highly medically literate.² As a result, meaningful access to educational materials about the Zika virus (for both patients and clinicians) might increasingly determine who gets screened. So too will clinical contexts: the difficulties in conducting Zika testing varies by region and institution, and while some clinicians will be able to rely on recommendations issued by their local jurisdiction, others will not. Additionally, many health care professionals have anecdotally reported the process of ordering tests for Zika to be arduous. Some may be inclined not to test in efforts to manage clinical burden, particularly in the face of the many competing screening and counseling responsibilities recommended during pre-natal care visits.

Access to prenatal care, patient and clinician information about Zika, and reproductive options in the face of a positive test result will vary by geography, education, and socioeconomic status. Further, access to testing may be driven by variability in insurance coverage. The average cost of Zika screening in September 2016 ranged from \$229 to \$800, according to one report.³ When testing is not clearly recommended by the CDC, insurance coverage might become a concern, and the extent to which different insurers will cover diagnostic testing for the Zika virus is uncertain. Given that the Zika epidemic is concentrated in lower-resourced populations with historically lower access to quality care, these new national guidelines may increase existing health disparities, as the population most likely to benefit from screening may not receive it.

Without recommendations for routine screening, responsibility for equitable access to serological testing will rely in large part on the clinical community ensuring access to information, robust shared decision making, and testing.

Second, there are concerns about surveillance, which will still be necessary for exposed but asymptomatic pregnant women whether or not serologic testing is performed, as these pregnancies and potential future children may need additional testing and intervention. Because 80% of Zika infections are asymptomatic, many pregnant women infected with the Zika virus will not be identified. Of concern, the proportion of birth defects identified among asymptomatic compared with symptomatic women was equal according to the US Zika Pregnancy Registry.⁴ However, large-scale data are lacking on variables such as length of exposure and specific site of exposure, which may help to stratify those asymptomatic

women who are most at risk, to guide informed decision-making around testing and follow-up. Ultrasound follow-up after Zika virus exposure is another area of uncertainty. The CDC recommends serologic testing of asymptomatic women if ultrasound abnormalities are identified; however, there is no guidance regarding when and if an additional ultrasound should be performed for patients who are potentially exposed to Zika but not serologically screened. Although most pregnant women undergo a routine ultrasound between 18 and 20 weeks, when an abnormality following a preconception infection with the Zika virus may be evident, ultrasound abnormalities from Zika may appear later in pregnancy. Emerging evidence indicates delayed manifestation of fetal anomalies are possible, including a report of a first-trimester Zika virus infection with normal fetal development by ultrasound between 14 and 20 weeks' gestation followed by sonographic evidence of congenital Zika syndrome noted at 29 weeks.⁵ As such, consideration should be given to an additional ultrasound in the third trimester even when midtrimester ultrasounds are normal.

Furthermore, newborns born without evidence of congenital Zika virus syndrome either antenatally or at birth may still be identified with neurodevelopmental abnormalities.⁶ Continuing to follow up these pregnancies and infants, as well as improving communication between obstetricians and pediatricians around Zika virus exposure, will be critical for ensuring that at-risk children are considered for head ultrasounds and ophthalmologic assessments for early diagnosis and intervention to mitigate harms from Zika-related neurologic disorders.¹

Third, limiting serologic testing for Zika virus sends the implicit message that the risk of Zika is minimal. Although the travel recommendations remain in place, the change in testing guidelines may be interpreted as suggesting that precautions about travel to Zika-affected areas during pregnancy are not as serious. While the Zika virus has certainly declined, the devastating consequences of infection during pregnancy warrant enduring education regarding prevention and risk from infection.

The CDC recommendations were written in response to the shifting state of the epidemic in the United States and the existing public health response tools. In addition to the need for refining and supplementing these interim guidelines, there is an urgent need to develop specific and sensitive diagnostics as well as effective vaccines and therapeutics, including products that will be acceptable for use in pregnancy.⁷ In the meantime, however, the current interim recommendations should be augmented by the clinical community, specifically around equitable use of shared decision making, appropriate use of third-trimester ultrasound surveillance, obstetrician-pediatrician communication of risk, and optimal follow-up for exposed but asymptomatic pregnant women and their children.

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